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Appeal Brief 10/20/99

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Richard M. Lawn, Gordon A. Vehar, and Karen L. Wion

Serial No: 08/444,934 Art Unit: 1653

Filed: May 22, 1995 Examiner: H. Schnizer

For: *METHODS AND DEOXYRIBONUCLEIC ACID FOR THE PREPARATION OF TISSUE FACTOR PROTEIN*

Assistant Commissioner for Patents
Washington, D.C. 20231

APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims 4-6, 8, 20, 21, 23-25, 27-29, and 31-41 in the Office Action mailed January 14, 1999, and maintained in the Advisory Action mailed August 11, 1999, in the above-identified patent application. A Notice of Appeal was mailed on June 10, 1999. A Petition for an Extension of Time for two months up to and including October 10, 1999, and the appropriate fee, and a check in the amount of $300.00 for the filing of this Appeal Brief is also enclosed.

(1) REAL PARTY IN INTEREST

The real parties in interest of this application are Genentech, Inc., the assignee, and the Licensees, Mt. Sinai Medical Center, Yale University and their subsidiary Dade Behring, Inc.

(2) RELATED APPEALS AND INTERFERENCES

There is a related Interference known to Appellants, the undersigned, or Appellants' assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal. Interference No. 103,203 is pending at the Board of Appeals and Interference and involves the determination of priority as to who was first to conceive and reduce to practice nucleic acid molecules encoding full length human tissue factor.

(3) STATUS OF CLAIMS ON APPEAL

Claims 4-6, 8, 20, 21, 23-25, 27-29, and 31-41 are pending. Claims 1-3, 7, 9-19 and 22, 26, and 30 have been cancelled. Claims 24 and 25 have been allowed. Claim 37 is objected to and claims 4-6, 8, 20, 21, 23, 27-29, and 31-41 are rejected and on appeal. The text of each claim on appeal, as amended, is set forth in Appendix I to this Appeal Brief.

(4) STATUS OF AMENDMENTS

The claims were last amended in the Amendment mailed February 18, 1997.

(5) SUMMARY OF THE INVENTION

Claims 4-6, 8, 31-36 and 38-41 are drawn to purified or recombinant human tissue factor protein having activity in a clotting assay, expressed from a nucleotide molecule encoding a tissue factor as shown in Figure 2, having an amino acid sequence from at least amino acid residue 1 to at least amino acid residue 219 or from at least amino acid residue one to at least amino acid residue 219 wherein an amino acid residue at an N- or O-glycosylation site is substituted. Claims 5, 32, and 33 specifically exclude the transmembrane domain.

Claims 20, 21, 23, 27, and 28 are drawn to soluble isolated tissue factor having activity in a clotting assay expressed from a nucleotide molecule encoding a tissue factor having the amino acid sequence shown in Figure 2 from amino acid 1 to an amino acid residue between amino acid residues 219 and amino acid residue 263. Claims 21, 28, and 34 define the molecule as not glycosylated.

Claims 27 and 35 are drawn to tissue factor as expressed in non-human cells.

Claims 29 and 37 are drawn to full length recombinant human tissue factor comprising the amino acid sequence shown in Figure 2 from amino acid 1 to amino acid 263, expressed in a non-human expression system.

Recombinantly produced human tissue factor and variants of human tissue factor are based on the cloning of the nucleotide molecules encoding human tissue factor (at least from page 9:line 28 to page 16:line 19). Human tissue factor is a protein involved in the complex signal transduction cascade responsible for the clotting of blood (page 2:line 1 to page 3:line 19). Tissue factor is an integral membrane bound protein which is associated with phospholipids *in vivo* (page 3:line 21 to page 5:line 5). Human tissue factor protein was very difficult to isolate and purify in quantities sufficient to determine the precise amino acid sequence and cDNA sequence encoding for human tissue factor because it is only present in very small quantities in human tissues (page 5:lines 23-34).

Oligonucleotide probes, designed from the partial amino acid sequence data available for tissue factor protein, were synthesized, and used to probe a placental cDNA library (Example 1).

cDNA clones which hybridized to these oligonucleotide probes were isolated, and were used to screen a human adipose cDNA library (Example 1). cDNA clones isolated from the human adipose library were further characterized. Northern blot analysis of placental mRNA revealed that the placental cDNA clones were only partial clones, but that four of the adipose cDNA clones were identical and contained full length human tissue factor (Examples 1 and 2). The isolated adipose cDNA sequence was shown to encode a membrane bound protein which contained an N-terminal leader sequence followed by a charged region which is followed by a hydrophobic core (page 35:lines 15-21). Methods for expressing recombinant human tissue factor from plasmids derived from the adipose cDNA clones of human tissue factor are disclosed (Example 3), along with specific clotting assays for determining whether or not the product of the expressed cDNA for human tissue factor is functional human tissue factor (Example 4).

A very extensive discussion of what human tissue factor variants are and how to obtain human tissue factor variants is provided (page 11:line 21 to page 16:line 19). All of the main categories of variants are described: variants derived by substitution, variants derived by insertion, and variants derived by deletion, as well as variants produced by expression in non-human cells, non-glycosylated variants, and variants having specific types of substitution such as the removal of cysteines to prevent disulfide bonds from forming. It was understood at the time the parent application was originally filed, February 12, 1987, that tissue factor consisted of an extracellular domain, a transmembrane domain, and a cytoplasmic domain (page 15:line 19 to page 16:line 5). As described by applicants, the transmembrane domain consists of

approximately 22 amino acids, from amino acid 220 to amino acid 242, of Figure 2 (page 15:line 22). The specification clearly discloses that removal of the hydrophobic regions of human tissue factor is a desired goal and that soluble tissue factor (i.e. not including the transmembrane domain) could be produced (page 15:lines 28-34).

(6) ISSUES ON APPEAL

The issue present on appeal is:

(1) whether claims 4-6, 8, 20, 21, 23, 27-29, 31-36 and 38-41 are sufficiently described in the specification under 35 U.S.C. § 112, first paragraph; whether claiming tissue factor proteins not expressly including the cytoplasmic domain are described in the application as originally filed.

(7) GROUPING OF CLAIMS

Appellants submit that the claims do not stand or fall together.

Group I

Claims 4, 6, 31, 32, 33, and 41 are drawn to purified or recombinant human tissue factor protein having activity in a clotting assay, expressed from a nucleotide molecule encoding a tissue factor shown in Figure 2, having an amino acid sequence from at least amino acid residue 1 to at least amino acid residue 219 or from at least amino acid residue 1 to at least amino acid residue 219 wherein an amino acid residue at an N- or O-glycosylation site is substituted.

Claims 5 and 32 specifically exclude the transmembrane domain defined by amino acid residues 220-243. Claims 6 and 33 specifically limit the tissue factor to residues 1-219.

Group II

Claims 8, 20, 21, 23, 27, 28, and 35 are drawn to recombinant tissue factor expressed in non-human cells.

Claim 21 is non-glycosylated tissue factor of claim 20, claim 27 limits the tissue factor of claim 20 to that specifically expressed in procaryotic cells, non-human animal cells, insect cells, plant cells, and yeast, and claim 28 is drawn to the tissue factor of claim 27 which is non-glycosylated.

Group III

Claims 29 and 37 are drawn to full length recombinant human tissue factor comprising the amino acid sequence shown in Figure 2 from amino acid 1 to amino acid 263.

Group IV

Claims 21, 28, and 34 are drawn to non-glycosylated tissue factor

Group V

Claims 38, 39, and 40 are drawn to recombinant human tissue factor protein having specific amino acid substitutions. Claim 36 defines a human tissue factor with an amino or carboxyl terminal fusion. Claim 38 defines a human tissue factor wherein the cysteine residues are substituted with other amino acids. Claim 39 defines a human tissue factor wherein the potential proteolysis sites are deleted by replacing the amino acids with glutaminyl or histidyl residues or deleting one of the basic residues. Claim 40 defines a human tissue factor wherein a residue at an N- or O-glycosylation site is substituted or deleted.

(8) ARGUMENTS

i. The Claimed Subject Matter

The claimed subject matter is drawn to recombinant human tissue factor variants. The application discloses the isolation and characterization of the cDNA encoding human tissue factor and human tissue factor protein. Multiple variants of human tissue factor are disclosed along with methods for producing variants of human tissue factor. As noted above, these variants can be divided into three groups:

(1) Variants where all or a portion of one or more of the domains has been deleted;

(2) Variants processed differently as a function of the expression system (for example, expressed in bacteria which do not glycosylate the protein); and

(3) Variants wherein specific amino acids have been substituted.

Only the first group has been rejected under 3 U.S.C. §112, first paragraph.

This application claims priority to an application filed February 12, 1987, a period when the manipulation of DNA was routine, once a gene or the cDNA had been obtained. Arguably the most revolutionizing technology for recombinant molecular biology had occurred nearly three years before, when the chemical synthesis of DNA was automated.[1] All of the necessary tools for making and using variants of a known protein were readily available by February 12, 1987. These tools included, for example, the enzymes needed to cleave and ligate pieces of

[1] Before the chemical synthesis of DNA and DNA sequencing, very few protein variants, as disclosed in this application, could be made at all. Once chemical synthesis of DNA was automated, however, the making of variants became accessible to almost any researcher.

DNA.[2] Once researchers could routinely synthesize oligonucleotides with any desired sequence, any variant could be made of any *known* DNA sequence.[3] By early 1985, a well-equipped lab could synthesize and sequence DNA. Thus, by 1987, the priority date of the present application, researchers were capable of making any variant of a given DNA sequence they desired. The key to performing this technology, however, was *knowing* the native sequence of the desired protein and the sequence of the cDNA that encoded it. Once the native sequence was known and the cDNA encoding the native protein was obtained, as it was for human tissue factor by the present applicants, the variants of the native protein were readily accessible.

Proteins are translated from an mRNA sequence which is read in the 5' to 3' direction. Proteins are coupled from amino group to carboxy group in a linear way. Thus, the first amino acid of a growing polypeptide chain, which later will become a specific protein, is the amino acid which forms the amino terminus. The last amino acid added to the growing polypeptide chain forms the carboxy end of the protein. As is discussed in the application and above, the amino terminus of tissue factor protein is a 32 amino acid signal peptide, which is followed by the extracellular portion of human tissue factor which is approximately 219 amino acids, which is

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[2] DNA restriction enzymes were first purified and used by Nathans and Smith. D. Nathans, Specific Cleavage of Simian Virus 40 DNA by Restriction endonucleases of Hemophilus influenzae, 68 Proc. Natl. Acad. Sci. USA 2913, (1971); D. Nathans, and H.O. Smith, Restriction endonucleases in the analysis of and restructuring of DNA molecules 44 Annu. Rev. Biochem. 273, (1975). DNA ligase was first purified by Gellert in 1967. S.B. Zimmerman et al., Enzymatic Joining of DNA Strands: a novel reaction of diphosphopyridine nucleotide, 57 Proc. Natl. Acad. Sci. USA 1841, (1967).

[3] Caruthers and co-workers chemically synthesized DNA in the mid-1970s. G.J. Powers et al., Optimal Strategies for the Chemical and Enzymatic Synthesis of Bihelical Deoxyribonucleic acids, 97(4) J. Am. Chem. Soc. 875, (1975). Automated chemical synthesis of DNA was available by the early 1980s. M. Hunkapillar et al., A Microchemical Facility for the Analysis and Synthesis of Genes and Proteins, 310

followed by the approximately 22 amino acid transmembrane portion, which is followed by the approximately 22 amino acid carboxy (intracellular) portion of human tissue factor. Thus, from the modular structure of human tissue factor and the order with which those modules are synthesized, the variants which are the subject matter of the present claims were readily apparent to one of skill in the art from reading the specification.

In 1987, researchers were well aware of the modular aspects of proteins, and understood that proteins often consisted of discreet domains which had discreet function.[4] This modularity of proteins provides certain insights to those of skill in the art. It was well known on February 12, 1987, to those of skill in the art that human tissue factor was a particular type of modular protein, an integral membrane protein.[5] It was also known that the extracellular portion of human tissue factor was the main functional unit with respect to human tissue factor's interaction with other proteins involved in the blood clotting cascade, although it was not known what structure this portion of tissue factor had nor its amino acid sequence. These facts created a distinct general picture of what human tissue factor protein looked like from a modular perspective for one of ordinary skill in the art (see for example, page 3 of the Advisory Action mailed May 17, 1999 and the 37 C.F.R. § 1.132 Declaration of Dr. Konigsberg). What was

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Nature 105 (1984).

[4] *See e.g.*, Brent et al., A bacterial repressor protein or a yeast transcriptional terminator can block upstream activation of a yeast gene, Nature, 314:198 (1985) and Brent et al., A bacterial repressor protein or a yeast transcriptional terminator can block upstream activation of a yeast gene, Nature, 312:612-5 (1984).

[5] See e.g., Bach R. et al., Purification and Characterization of Bovine Tissue Factor, J. Biol. Chem. 256:8324-8331 (1981).

missing, however, was the DNA sequence that encoded the specific protein sequence that made up each of the tissue factor domains or modules. This was provided by the applicants. Once this information was obtained and the cloned cDNA was isolated, the information about the modularity of human tissue factor and the knowledge regarding protein modifications known to those of skill in the art could be combined to arrive at the presently claimed subject matter.

ii. Rejections Under 35 U.S.C. § 112, first paragraph.

1. Legal analysis of 35 U.S.C. § 112, description requirement

The standard regarding what is or is not supported by the specification has been clearly articulated as requiring the specification to convey with reasonable clarity to those skilled in the art that, as of the priority date (February 12, 1987) the inventor was in possession of the invention, i.e., whatever is now claimed. Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555 19 USPQ2d 1111, 1117 (Fed . Cir. 1991). MPEP § 2163.02 also describes the standard to be applied in determining if the written description requirement is satisfied. MPEP § 2163.02 reads, in pertinent part:

> Whenever the issue [of adequacy of the written description] arises, the fundamental factual inquiry is whether *a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed.* The subject matter of the claim *need not be described literally* (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement. (emphasis added).

Thus, the subject matter does not "need to be described literally," it merely needs to have been "conveyed to those skilled in the art." Id.

The application of the description requirement must be done on a "case by case basis." Ralston Purina Co. v. Far-Mar-Co., Inc. 772 F.2d 1570, 277 USPQ 177 (Fed. Cir. 1985). The issue in Ralston Purina Co. revolved around the type of disclosure that was necessary to support specific embodiments when only general ranges were disclosed in the application. For example, the claims at issue in Ralston Purina Co. contained the following limitations: (1) in excess of 212° F.; (2) at least about 212°F.; (3) substantially above 212° F.; (4) substantially in excess of 212° F.; and (5) into the range of 212° -310° F. Ralston Purina Co. v. Far-Mar-Co., Inc. at 1570. The only support the priority disclosure provided was the statement "[a mixture] must be subjected to heat" and Example 1 provided the range: 212° - 380° F. The trial court found all of the claim limitations discussed above supported by the priority disclosure because expert testimony indicated that one of ordinary skill in the art would not consider 380° an upper limit, but rather would consider whatever temperature the material burned at to be the upper limit. In addition it was found that the range 212° -310° was adequately described because it involved nothing "more than . . . that which had been described earlier." A number of important concepts can be identified in this Federal Circuit decision.

First, the expert testimony as to what one of ordinary skill in the art would judge to be described is valid and powerful evidence as to what the application truly does describe. Second, as long as one of ordinary skill in the art would recognize lower boundaries of some defined range as describing a lower limit, an open ended claim is sufficiently described if a naturally occurring inherent upper boundary would be understood by the ordinary skilled person. Third,

the barometer for judging the adequacy of the description within an application is what one of ordinary skill in the art would understand to be described.

In re Winkhaus, 188 U.S.P.Q. 129 (CCPA 1975), states, "a person skilled in the art might realize from reading the disclosure that such a step is possible is not a sufficient indication to that person that the step is part of . . . [the] invention." Id. at 131. In re Winkhaus does **not** apply to situations where the element of the claim is disclosed, and the issue is whether or not the specific language used in the claim is described. The facts in Winkhaus are clear. The Appellants attempted to add an additional element to the claim on appeal, and there was no description with respect to that element. The Appellants argued that because it would have been obvious to add the element, the element was not new matter. This is completely different than the present situation where the issue is what the description in the application means to one of skill in the art, not whether or not it would have been obvious to make the claimed variants.

In so far as the Examiner is relying on Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d. 1398 (CAFC 1997), as the basis for this rejection, Appellants note that Regents of U.C. is not applicable since the claims and underlying specification here are not analogous to the facts there. The Court in Regents of U.C. relied on the fact that the description of example 6 in the patent at issue prophetically described obtaining a cDNA sequence from the **protein** sequence of the human protein. This is completely different than the situation here, where the issue is what one of skill in the art would understand to be described by the specification. This difference is absolutely critical because the court in Regents of U.C. relied on

their own precedent of In re Deuel, 51 F.3d 1552, 1558, 34 USPQ2d 1210, 1215 (1995). The court stated, "A prior art disclosure of the **amino acid sequence** of a protein does not necessarily render particular DNA molecules encoding the protein obvious because the redundancy of the genetic code permits one to hypothesize an enormous number of DNA sequences encoding for the protein." In relying on the relationship of amino acid sequence to nucleic acid sequence, Regents of U.C. is limited to protein-to-DNA situations.

It should be noted that the court in Regents of U.C. did not specifically address (and thus, did not overrule) the standard that has been accepted for the description requirement for the last 125 years, most recently explicated in Vas-Cath Inc. v Mahurkar. Notwithstanding the above, it is noted that only decisions handed down by an *en banc* panel of the Federal Circuit are sufficient to overrule previous case law. In this respect, the decisions of the Federal Circuit in U.C. Regents and its progenitor cases do not overrule the longstanding positions taken by the courts on the description requirements. (Vas-Cath Inc. v Mahurkar).

2. The specification fully supports the claimed variants

Claims to variants are discussed in the specification at least on page 6, lines 10-13, and lines 18-27; page 9, lines 12-25; page 13, lines 4-5; from page 13, line 35, to page 14, line 5; Figure 2; and Figure 5. Specific support for the recited amino acid range (from amino acid 1 to amino acid 219) is provided by Figure 5 where this region is depicted as the first open bar, the indication (on page 9) that the filled bar in Figure 5 begins at amino acid residue 220, the disclosure that deletion variants of human tissue factor protein are specifically contemplated

(see, for example, page 11, lines 21-23; from page 12, line 31, to page 13, line 16; from page 15, line 19, to page 16, line 5), and the indication that deletion variants of tissue factor protein having substantial portions deleted are specifically contemplated (see, for example, the first full paragraph of page 13 where variant tissue factor fragments having as few as 100 residues are specifically discussed).

Support for claims 32 and 33 appears at least on page 15, lines 20-27. Support for claim 34 appears at least on page 16, lines 11-13. Support for claim 35 appears at least on pages 19-22, and especially on page 22, lines 11-12. Support for claim 36 appears at least on page 11, lines 21-32; and page 6, lines 24-25. Applicants note that the cited passage on page 6 specifically indicates generic fusions as an alternative to either a methionine fusion or a signal sequence fusion. Support for claim 37 appears at least in the paragraph bridging pages 10 and 11. Support for claims 38-40 appears at least in the first full paragraph on page 16.

Aside from what is explicitly described common sense makes clear that the Examiner's position is contradictory to the understanding of those skilled in the art. There was no known function for the cytoplasmic domain. The easiest way to delete the transmembrane region was to make a construct that simply stopped at amino acid 219, thereby deleting both the transmembrane domain and the cytoplasmic domain, or any portion thereof. The Examiner's interpretation that one would add back in the DNA sequence encoding the cytoplasmic domain, not known to serve any function, therefore makes no sense.

The present rejection is based, essentially, on the contention that the specification does not describe what is claimed so as to reasonably convey to one skilled in the art that applicants were in possession of the claimed tissue factor proteins at the time the application was filed. The rejection specifically asserts (page 2) that the specification is limited to descriptions of tissue factor variants that (1) lack residues 220-242, (2) have specific insertions, (3) have specific point mutations, or (4) have altered glycosylation sites.

The standard regarding what is or is not supported by the specification has been clearly articulated as requiring the specification to convey with reasonable clarity to those skilled in the art that, as of the filing date sought, the inventor was in possession of the invention, i.e., whatever is now claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555 19 USPQ2d 1111, 1117 (Fed . Cir. 1991). In this regard, applicant also directs attention to MPEP § 2163.02 which describes the standard to be applied in determining if the written description requirement is satisfied. MPEP § 2163.02 reads, in pertinent part:

> Whenever the issue [of adequacy of the written description] arises, the fundamental factual inquiry is whether *a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed.* The subject matter of the claim *need not be described literally* (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement. (emphasis added)

Applicants note that the specification indicates that deletions of the transmembrane domain are not considered to be limited to deletion of only the specific amino acids of the transmembrane domain. For example, in the first full paragraph on page 15, the specification states that "a major *class* of substitutional or deletional variants *are those involving* the

transmembrane, i.e. hydrophobic or lipophilic, region of tissue factor protein" (emphasis added). Applicants assert that this sentence clearly conveys that applicants contemplated deletion variants which include both the deletion of the transmembrane region and deletion of other amino acids. The application as a whole identifies the N-terminal region of tissue factor from amino acids 1 to 219 as a separate unit of tissue factor. For example, in Figure 5 the region from amino acid 1 to 219 is depicted as the first open bar, and page 9 indicates that the filled bar in Figure 5 begins at amino acid residue 220.

3. Konigsberg declaration clearly indicates that the claims are described in the specification

The issue on appeal is whether the specification adequately described human tissue factor variants with amino acid sequence one to between 219 and 263, i.e., variants not including all or part of the transmembrane domain and/or all or part of the cytoplasmic domain. These domains are clearly depicted in Figure 2 and further by reference to the hydropathy profile of Figure 5. The Examiner's position is that the specification only supports claims to full length human tissue factor (1-263) or human tissue factor including all the extracellular domain (1-219) and all the cytoplasmic domain (244-263).

Two documents were submitted to establish that the specification teaches one skilled in the art to delete all or a portion of the transmembrane region (and cytoplasmic domain):

(1) The declaration of Dr. William Konigsberg, an expert in cloning and human tissue factor in 1987; and

(2) The opposition filed by Diagnostica Stago in the corresponding European patent.

It is the opinion of both that the claims to the variants, including those in dispute, are fully described and enabled.

Page 7 of the Advisory Action dated, August 11, 1999 at the first full paragraph sums up the position taken by the Examiner. The Examiner refuses to give any weight to the Konigsberg Declaration. The Examiner states, "Konigsberg's statement that deletion of the TMD [transmembrane domain] indicates that the inventors contemplated deletion of both the TMD and the ICD [intra-cellular domain] is speculative in the absence of the disclosure in the specification of the deletion of both domains."

a. <u>Dr. Konigsberg's Declaration</u>

Dr. Konigsberg is an acknowledged expert on tissue factor, its production, and its isolation (A copy of Dr. Konigsberg's Declaration and *Curriculum Vitae* accompanies this Appeal Brief for the convenience of the Board). Dr. Konigsberg's statements as to the extent and sufficiency of the specification are certainly more than "speculative" given his position in the field.

The Konigsberg Declaration indicates that one of ordinary skill in the art at the time the application was filed would know that the transmembrane domain would bridge the extracellular regions and the cytoplasmic regions (this is also supported by the application as discussed above). Furthermore, Dr. Konigsberg goes on to state that those of skill in the art understood that the "extracellular domain could be used separately from both the transmembrane region and

the cytoplasmic region." (Konigsberg Declaration at 3). Dr. Konigsberg sums up the knowledge of one of ordinary skill in the art at the time of the priority application by saying,

> "it is clear, those of skill in the art at the time would have understood, that deletion of the transmembrane region **is equivalent** to deletion of both the transmembrane region and cytoplasmic region, since the cytoplasmic domain serves no purpose in the absence of the transmembrane domain."

(Konigsberg Declaration at 4, emphasis added).

It is clear, notwithstanding the Examiner's arguments, that Dr. Konigsberg provided factual statements based on his reading of the application and on the knowledge of one of skill in the art and that he attempted to indicate that one of ordinary skill in the art would know that the deletion of the transmembrane domain referred to the deletion of the carboxyterminal portion of the protein that contained the transmembrane domain.

b. Legal analysis of 1.132 Declarations

A declaration under 37 C.F.R. § 1.132 may be submitted to the patent office to overcome a rejection based on "facts within the personal knowledge of" an Examiner. The issue presented in this Appeal is whether an Examiner can dismiss the factual statements made by an expert in a C.F.R. § 1.132 Declaration. In re Alton 76 F.3d 1168 (Fed. Cir. 1996) is a recent decision by the Federal Circuit on this issue in an area of technology closely related to the presently claimed technology. The applicants in In re Alton claimed a variant of human interferon that had three amino acids deleted and one amino acid added, relative to the native protein. Id. at 1170 The closest support in the priority application was an example that specifically recited a variant that

contained the *same* three deleted amino acids, the *same* additional amino acid, but also contained a single substitution at a *different* amino acid. Id. at 1171. Thus, there was not literal support for the elements of the claim at issue.

The applicants used a Declaration under 37 C.F.R. § 1.132 in support of the assertion that the specification would be understood by one of skill in the art to have disclosed the claimed variant. Id. The declaration stated in part, "It is my opinion that a skilled worker in molecular biology and the cloning and expression of genes, would, in, 1983 have understood the proposed modification . . . [in the claim at issue] to have been described independently of any suggestion to . . . [make the other modification described in the application]." The Examiner rejected the declaration because according to the Examiner, "the Declaration does not point to inherent support or evidence to support the conclusory statement . . . [and l]ittle weight is given an opinion affidavit on the ultimate legal question at issue." The court resoundingly rejected this reasoning holding as error the, "(1) viewing [of] the [] declaration as opinion evidence addressing a question of law rather than a question of fact; and (2) the summary dismissal of the declaration, without an adequate explanation of why the declaration failed to rebut the Board's prima facie case of inadequate description." Id. at 1174. In support of this holding the court focused on the fact that the Examiner's assertion that the affidavit was merely opinion, thus meriting little weight. The court stated,

> [W]e do not read the declaration as asserting an opinion . . . on patentability . . . . Rather the declaration is offering factual evidence in an attempt to explain *why* one of ordinary skill in the are would have understood the specification to describe the

> modification involving the deletion of the first three amino acids independently of the modification at . . . [the other] position. [The declarant's] use of the words 'it is my opinion' to preface what someone of ordinary skill in the art would have known does not transform the factual statements contained in the declaration into opinion testimony."

Id. at 1174-5. (emphasis in original)

In addition, the court strongly indicated that the PTO, in a case such as this where the issue is not whether the subject matter is discussed at all, but rather is whether the subject matter is discussed specifically, *must* provide *reasons* why the claimed subject matter would not be understood by one of ordinary skill in the art as being described. The court stated, "

> [T]he burden placed on the examiner varies, depending upon what the applicant claims. . . . If the specification contains a description of the claimed invention, albeit not *in ipsis verbis* (in the identical words), then the examiner or the Board, in order to meet the burden of proof, must provide reasons why one of ordinary skill in the art would not consider the description sufficient.

Id. at 1175 (*citing* In re Wertheim, 541 F.2d 263, 264 (C.C.P.A. 1976)). The court understood that the Examiner's rejection amounted to a rejection for not explicitly reciting the claimed variant and in addition understood that this analysis is non-responsive to a Declaration submitted which presents reasons *why* one of ordinary skill in the art understands the full extent of an application's description. Id. at 1176. Thus, declarations under 37 C.F.R. § 1.132 which express an "opinion" as to how one of skill in the art would read an application *are not* to be dismissed as mere opinion evidence when the declaration presents factual information upon which the opinion is based.

c. The Konigsberg Declaration presents facts

The Konigsberg declaration presents numerous factual statements regarding the art and the state of the art. Dr. Konigsberg states,

> At the time, it was understood that transmembrane proteins generally functioned in one of two ways. In the first, the main activity of the protein resides in the extracellular domain, with the transmembrane domain serving to merely anchor the extracellular domain. In this scheme, the cytoplasmic domain is essentially irrelevant except for the first two basic residues which serve to help anchor the hydrophobic sequence that spans the membrane. In the second scheme, the transmembrane region serves as conduit for conducting signals between the extracellular domain and the cytoplasmic domain. Receptor proteins are (and were) a well-known example of this type of transmembrane protein. When a ligand binds to the extracellular domain of a receptor protein, this binding is communicated to the cytoplasmic domain via the transmembrane domain (thereby propagating an external signal to the inside of the cell).

Id. at 4-5.

These factual statements provide the basis for Dr. Konigsberg's conclusion as an expert.

> From this scheme, it is clear, and those of skill in the art at the time would have understood, that deletion of the transmembrane region is equivalent to deletion of both the transmembrane region and the cytoplasmic region, since the cytoplasmic domain serves no purpose in the absence of the transmembrane domain. For these reasons, it is my opinion that those of skill in the art at the time the application was filed would have considered the reference to deletion of the transmembrane region to indicate that the inventors contemplated deletion of the C-terminal portion of tissue factor, including the cytoplasmic domain.

Id. at 5.

It is unequivocal that Dr. Konigsberg's opinion is based on the factual statements that he presented. The Examiner's rejection, however, has dismissed the factual statements of the

Konigsberg declaration as mere opinion and furthermore has provided no evidence which refutes the factual statements provided by Dr. Konigsberg. As In re Alton indicates, the Examiner is required to provided factual evidence rebutting the factual assertions and conclusory statements of a 37 C.F.R. § 1.132 declarant. The Examiner's argument is best summed up in a passage from the Advisory action mailed May 17, 1999. The Examiner states,

> These passages [referring to the factual statements above] do not state that Applicants describe the ECD [extracellular domain] by itself but that the deletion of the TMD [transmembrane domain] would indicate to those of skill in the art that the ECD could be used by itself. While the Examiner agrees that deletion of the TMD is equivalent functionally to the deletion of both the TMD and the ICD, the structure of the resulting proteins is different.

Id. at 7.

The Examiner agrees that Dr. Konigsberg's declaration provides factual statements regarding the state of the art the time of the application and that these statements are correct. The burden on the Examiner, however, is to provide factual evidence rebutting these statements. This has not been provided. The issue is what one of ordinary skill in the art would have understood to be in the possession of the inventors at the time the application was filed. Dr. Konigsberg provides information on this point and the Examiner agrees with it, but inexplicably continues to maintain the rejection because neither Konigsberg or the specification "describe the ECD [extracellular domain] by itself." Advisory Action mailed May 17, 1999 at 7. There is no requirement for *in ipsis verbis* support and this is the type of support, by admission, that the Examiner is requiring. In re Wertheim at 264.

Just as in the declaration at issue in In re Alton, the declaration in the present application is directly aimed at providing information as to *why* one of skill in the art would have understood the application to have disclosed tissue factor variants comprising amino acids 1 to between 219 and 263. As pointed out by Dr. Konigsberg, the understanding that tissue factor is a modular protein coupled with the knowledge that the extracellular region was important for function is the *why*. Given this knowledge not only would one of ordinary skill in the art understand that a description of the deletion of the transmembrane domain described the claimed molecules but it is very likely the *only* way that one of skill would view it because of the ingrained knowledge of what tissue factor was and is, a modular protein with a specifically functional extracellular domain.

4. The Diagnostics Stago Opposition

The corresponding European patent was allowed with claims encompassing the variants including amino acid one to between 219 and 263. Two oppositions were filed. One opposed the patent on the basis of insufficient disclosure. In response, the second Opponent, made the gratuitous statement that of course the application was enabling but that it was obvious in view of the prior art. A copy of this opposition is enclosed to facilitate the Board's review.

The Examiner ignored this evidence, which is clearly relevant to the question of how one skilled in the art would interpret the specification.

5. The Groups are separately patentable

a. Group I

Claims 4, 5, 6, 31, 32, 33, and 41 are all drawn to the variants discussed above. No further discussion is necessary.

b. Group II

Claims 8, 20, 21, 23, 27, 28, and 35 are drawn to tissue factor expressed in non-human expression systems. No rejection has been made that this subject matter is not enabled or adequately described.

c. Group III

Claims 29 and 37 are drawn to recombinant human tissue factor comprising the amino acid sequence shown in Figure 2 from amino acid one to amino acid 263. The Examiner has acknowledged that the full length tissue factor protein is enabled and fully described. Both of these claims should be allowed (or allowable).

d. Group IV

Claims 21, 28, and 34 are drawn to non-glycosylated tissue factor. No rejection has been made that this subject matter is not enabled or adequately described.

e. Group V

Claims 38, 39, and 40 are all drawn to specific amino acid substitutions. No rejections that this subject matter is not enabled or adequately described has been made. Claims 24 and 25

are also drawn to specific amino acid substitutions. However, claims 24 and 25 are allowed and are not in issue in this appeal.

6. Summary

The specification provides explicit support for a variety of deletion variants.

Appellants have provided evidence in the form of Dr. Konigsberg's Declaration and the opposition by Diagnostica Stago that those skilled in the art would understand the specification describes the variants defined by the claims.

The Examiner has provided no factual evidence to rebut Appellant's proof.

(9) CONCLUSION

In conclusion, the subject matter of claims 4-6, 8, 20, 21, 23, 27-29, and 31-41 are adequately and clearly described in the specification under 35 U.S.C. § 112, first paragraph.

Respectfully submitted,

Robert A. Hodges
Reg. No. 41,074

Date: October 12, 1999

ARNALL GOLDEN & GREGORY, LLP
2800 One Atlantic Center
1201 West Peachtree Street
Atlanta, Georgia 30309-3450
(404) 873-8796
(404) 873-8797 (fax)

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Jean Hicks

Jean Hicks

Date: October 12, 1999

APPENDIX: Claims on appeal:

4. Purified human tissue factor protein expressed from a nucleotide molecule encoding a tissue factor selected from the group consisting of tissue factor having an amino acid sequence as provided in Figure 2 from at least amino acid residue one to at least amino acid residue 219, and human tissue factor having an amino acid sequence as provided in Figure 2 from at least amino acid residue one to at least amino acid residue 219 wherein an amino acid residue at an N- or O-glycosylation site is substituted, wherein the tissue factor has activity in a clotting assay with human plasma.

5. The tissue factor protein of claim 4 wherein the nucleotide molecule does not encode the transmembrane domain defined by amino acids 220 to 243 as provided in Figure 2.

6. The tissue factor protein of claim 4 wherein the nucleotide molecule encodes a tissue factor having an amino acid sequence as provided in Figure 2 from amino acid residue one to amino acid residue 219.

8. The tissue factor protein of claim 4 having an amino acid sequence as provided in Figure 2 and expressed in a recombinant non-human host cell.

20. A soluble isolated tissue factor expressed from a nucleotide molecule encoding tissue factor in a recombinant non-human host cell, the tissue factor having the amino acid sequence shown in Figure 2 from amino acid one to an amino acid residue between amino acid residues 219 and amino acid residue 263, wherein the tissue factor has activity in a clotting assay.

21. The tissue factor of claim 20 which is not glycosylated.

23. The tissue factor of claim 20 having an amino acid sequence of Figure 2 from between amino acid one and between residues 220 and 263.

24. A tissue factor comprising the amino acid sequence shown in Figure 2 wherein the cysteine residues are substituted with other amino acids.

25. A tissue factor comprising the amino acid sequence shown in Figure 2 wherein the potential proteolysis sites are deleted by replacing the amino acids with glutaminyl or histidyl residues or deleting one of the basic residues.

27. The recombinant human tissue factor of claim 20 expressed in a host cell selected from the group consisting of procaryotic cells, non-human animal cells, insect cells, plant cells, and yeast, having activity in a clotting assay.

28. The recombinant human tissue factor of claim 27 which is not glycosylated.

29. The recombinant human tissue factor of claim 27 comprising the amino acid sequence shown in Figure 2 from amino acid residue one to amino acid residue 263.

31. Recombinant human tissue factor protein expressed from a nucleotide sequence encoding an amino acid sequence comprising from amino acid residue one to amino acid residue 219 as provided in Figure 2, wherein the tissue factor protein has activity in a clotting assay with human plasma.

32. The recombinant human tissue factor protein of claim 31 wherein the nucleotide sequence does not encode the transmembrane domain of human tissue factor.

33. The recombinant human tissue factor protein of claim 32 wherein the nucleotide sequence does not encode the amino acid sequence from amino acid residue 220 to amino acid residue 243 as provided in Figure 2.

34. The recombinant human tissue factor protein of claim 31 which is not glycosylated.

35. The recombinant human tissue factor protein of claim 31 which is expressed in a host cell selected from the group consisting of procaryotic cells, non-human animal cells, insect cells, plant cells, and yeast.

36. The recombinant human tissue factor protein of claim 31 which includes an amino or carboxyl terminal fusion.

37. The recombinant human tissue factor protein of claim 31 wherein the amino acid sequence consists of from amino acid 1 to amino acid 263 as provided in Figure 2.

38. The tissue factor of claim 31 wherein the cysteine residues are substituted with other amino acids.

39. The tissue factor of claim 31 wherein the potential proteolysis sites are deleted by replacing the amino acids with glutaminyl or histidyl residues or deleting one of the basic residues.

40. The tissue factor of claim 31 wherein a residue at an N- or O-glycosylation site is substituted or deleted.

41. Recombinant human tissue factor protein comprising an amino acid sequence from amino acid residue one to amino acid residue 219 as provided in Figure 2, wherein the tissue factor protein has activity in a clotting assay with human plasma.

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Certificate of Mailing

Appendix: Claims on Appeal

Copies of:

Konigsberg Declaration

Opposition by Diagnostica Stago